Performing the Brain Death Examination and the Declaration of Pediatric Brain Death

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Abstract

Declaration of brain death is a clinical diagnosis made by the absence of neurological function in a comatose patient secondary to a known irreversible cause. Brain death determination is not an infrequent process in pediatric intensive care units. It is important that pediatric intensive care providers understand the definition of brain death and intensivists are able to implement brain death testing. The following is a narration detailing the process of brain death determination by physical examination. First, the prerequisites that determine patients' eligibility for brain death testing will be outlined. Next, each part of the physical exam, including the apnea test, will be described in detail. Finally, how the declaration of brain death is made is stated. In addition, special considerations and ancillary testing will be briefly highlighted.

Keywords

- pediatric
- brain death
- exam

Introduction

Declaration of brain death in the pediatric population is governed by specific criteria and detailed physical examination. Brain death is a clinical diagnosis based on the absence of neurological function with a known irreversible cause of coma. Although there are no universal worldwide accepted guidelines for brain death determination, the majority of developed countries agree that brain death is medical and legal death.[1] The concept of brain death was first introduced by the French neurophysiologists Mollaret and Goulon in 1959. They proposed that *le coma depasse* was a state beyond coma that included loss of motor activity, sensation, consciousness, and vegetative functions. In 1968, an ad hoc committee of the Harvard Medical School published the first definition of death using neurological criteria.[2] Since these publications, numerous expert groups have issued guidelines for the declaration of brain death. In the United States, the National Conference of Commissioners on Uniform State Laws, with the support of the American Medical Association and the American Bar Association, drafted Uniform Determination of Death Act in 1980 to provide legal support for the neurological determination of death. This act states that an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.[3] It does not prescribe the manner in which the cessation of brain function is determined, rather leaves it to the medical community to set medical criteria for declaration of brain death. The American Academy of Pediatrics (AAP) published guidelines in 1987 to aid physicians in the determination of brain death in infants and children.[4] In 2011, multiple societies, including the Society of Critical Care Medicine and the Child Neurology Society, endorsed new brain death guidelines.

The declaration of brain death is not an uncommon occurrence in the pediatric intensive care unit (PICU), with a 0.9% mortality rate for of all PICU admissions.[5]

In a recent prospective case series of five U.S. teaching hospitals, brain death was the mode of death in 16% of all deaths in the PICU.[6] A retrospective review of deaths in a tertiary United Kingdom PICU over a 10-year period found that brain death was the mode of death in 24% of patients.[7] Determining brain death is important for several reasons, patients who have progressed from neurological injury to brain death require significant resources to maintain cardiorespiratory function. These resources can be allocated to patients with potential for recovery. Furthermore, brain-dead

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patients provide the majority of organs for transplantation.[8] In addition, delaying brain death determination can add increased stress to the patient's family.[9]

The following description of the brain death examination will outline the process of determination of brain death by physical examination. There are prerequisites that the patient must meet before brain death testing can commence. Once these are met, a physical exam is completed to evaluate neurological function and finally an apnea test.

Prerequisites for Brain Death Declaration

To proceed with the brain death examination, the patient must have sustained a neurological injury capable of causing neurological death. This prerequisite is included not only in the guidelines published by the AAP[4] but also by the Canadian forum recommendations.[10] The AAP guidelines state that neuroimaging, while not necessary to obtain, can be useful as evidence of central nervous system (CNS) injury should be found on computed tomography or magnetic resonance imaging. Conditions that can mimic brain death or reversible causes of coma must be absent. Some of the more common reversible causes for coma that must be excluded include unresuscitated shock, severe metabolic disorders, severe electrolyte abnormalities, and significant drug intoxications. Other potential causes include locked-in syndrome, Guillain–Barre, brain stem encephalitis, and high spinal cord injury.

Hypothermia is another potential cause of abnormal neurological exam as it depresses the CNS, can cause apnea, and delay drug metabolism.[11] As therapeutic hypothermia is increasingly used after neurological injury, neurological examination should be delayed until after rewarming.[12,13] Current literature suggests that a minimum observation period should be observed following hypothermia. Most recommend 72 hours, as the brain death exam and other neurological assessments could be unreliable.[11,13,14] The patient's core body temperature should be more than 35°C.[4] Normothermia may be achieved by using a warming blanket.[15]

Sedation and analgesic medications as well as antiepileptics and neuromuscular blockers are commonly used in the care of the critically ill patient and may affect the neurological exam. Medications in these classes that can cause sedation should be discontinued and time from discontinuation of medication to brain death exam should be determined by using the medication half-life.[3,4,10] If available, serum levels of drugs should be in the low-to-mid therapeutic range before beginning the brain death exam. Neuromuscular blockade clearance can be confirmed by using a nerve stimulator to evoke a sustained "train of four" muscle twitch.[3]

Immediately following cardiopulmonary resuscitation or other severe acute brain injuries assessment of neurological function may be unreliable, brain death assessments should be deferred for at least 24 to 48 hours or longer if variability in exams.[3,10] However, once the etiology of coma/unconsciousness is determined, established that the patient's condition is irreversible, confounders eliminated or corrected, and above prerequisites are met, the first clinical exam may be performed. In the pediatric population, two examinations each with an apnea test separated by an observational period are required. The two examinations should be performed by two different physicians; the apnea test may be conducted by each physician performing the clinical exam. The examinations are separated by an observation period. For term neonates ($\geq$ 37 weeks' gestation) up to 30 days old, the observation period is 24 hours, and for infants $>$ 30 days old to children 18 years of age, only a 12-hour observation period is required. The first examination is to establish that the patient has met neurological criteria for brain death. The second examination confirms brain death.[4]

Clinical Exam

The goal of the clinical exam is to establish cessation of all brain and brain stem function. This can be accomplished with a thorough neurological examination which includes testing of high neurological function, cranial nerve (CN) function, and presence of brain stem reflexes. Testing of high neurological function consists of determining complete loss of consciousness. This requires the patient to be unresponsive to all stimulation mediated above the spinal cord. Flaccid muscle tone should be demonstrated on passive range of motion of extremities. Spontaneous eye opening or eye movement should be absent.[15] The patient should not respond to noxious stimuli, there should be no motor response, such as purposeful movement and facial grimacing, except for spinal reflexes. Examples of noxious stimuli include sternal rub, supraorbital pressure, deep nail bed pressure, and pinching.[16] A Glasgow coma scale score of 3 (no eye opening, verbal response, or movement either spontaneous or in response to stimulation) is indicative of loss of consciousness.[17]

Spinal cord events present as a wide range of movements that are reflexive, but can appear to be spontaneous and purposeful to caregivers and family members. In brain death literature, there have been several mechanisms suggested for the etiology of spinal reflexes; however, the exact pathophysiology is unknown. A recent cross-sectional observational study found that at least one-third of patients declared brain dead exhibited at least one type of spinal reflex. The most common reflexes, in order, are plantar response, myoclonus, triple flexion reflex and pronator extension reflex, and undulating toe reflex. Furthermore, it was found that patients who had become hemodynamically stable after medical intervention often were more likely to have spinal reflexes.[18] Caregivers and family members should be informed and educated about these reflexes; they can seem purposeful and raise suspicion about the diagnosis of brain death. This misperception can have a negative effect on obtaining consent for organ donation.

CN function is accomplished by clinical examination of CNs II to X, which assesses for the presence of several brain stem reflexes, pupillary light reflex, corneal reflex, movement of facial muscles, oculocephalic reflex, oculovestibular reflex, and the gag and cough reflexes. The pupillary light reflex assesses CNs II and III, the optic and oculomotor nerves, respectively, as well as the midbrain. The examiner should assess pupillary size and shape in a dimly lit room. A bright light is shined into each

eye to determine pupillary response or lack of response. In brain death, the pupils should be midsized or dilated, approximately 4 to 9 mm and nonreactive to light.[16,17] It also should be noted that in patients with severe facial trauma or ocular trauma and those with preexisting pupillary abnormalities, this test may be unreliable or inconclusive, and an ancillary test should be entertained.[16]

The corneal reflex assesses CNs III, V, and VII (oculomotor, trigeminal, and facial nerves, respectively) and the pons. This is done by lightly touching the cornea on each eye with a cotton swab or piece of gauze.[16] The eye lids are gently held open, so as not to prevent potential blinking. The absence of blinking or eye movement is consistent with brain death. CNs V and VII can also be assessed by supraorbital pressure or pressure on bilateral condyles of the temporomandibular joints. The absence of facial movement is expected with brain death.[4]

Oculocephalic and oculovestibular reflex testing assesses CNs III, IV, and VII (oculomotor, trochlear, and vestibulocochlear nerves), pons, and midbrain. The oculovestibular reflex also assesses function of CN VI, the abducens nerve. The oculocephalic reflex, commonly known as the doll's eyes reflex, is tested by rotating the patient's head quickly side to side while holding the eyes opening to observe eye movements relative to the orbit. Eyes will stay midline with rotation in the case of brain death. It is important to rule out cervical spine injury prior to performing the examination of the oculocephalic reflex. If cervical spine injury cannot be excluded, this portion of the exam should not be performed. However, the brain death exam can proceed by testing the oculovestibular reflex as the same CNs, as well as CN IV, and areas of the brain stem are tested.[16] The oculovestibular reflex is tested using the cold caloric test. To proceed with cold caloric, the examiner must ensure the patency of the external auditory ear canals and verify that the tympanic membranes are intact bilaterally. The patient is then positioned with the head of the bed elevated at 30 degrees. Ice–cold water (~33°C) is instilled into one external auditory ear canal, both eyes are held open to observe for movement. The water may be instilled using a syringe with an intravenous catheter (with the needle removed) attached and placed just inside the auditory canal. Each canal should be assessed independently. The patient's eyes should be observed for 1 minute per side, absence of movement is consistent with brain death.[4]

CNs IX and X, the glossopharyngeal and vagus nerves, as well as the medulla may be tested by attempting to elicit the gag and cough reflexes. To attempt to evoke the gag reflex, the examiner should use a tongue depressor or suction device to stimulate the posterior pharynx, being mindful to not dislodge the patient's endotracheal tube (ETT). This stimulation will not produce a response from the brain-dead patient.[4,15–17] The cough reflex may be tested by advancing a suction catheter down the ETT to the level of the carina. One or two suction passes should be made. The patient should have no response in brain death.[4,15–17]

Apnea Test

The apnea test confirms the loss of spontaneous respirations as well as a neurological drive to breath.[15,16] If a cause of coma has been identified and the examination of the CNs and brain stem reflexes is consistent with brain death, the examiner should proceed to apnea testing. The apnea test must be performed with each neurological examination to ensure that coma and apnea coexist.[3] The patient must meet certain prerequisites before the apnea test can be performed. These prerequisites attempt to ensure that the patient will remain stable and not incur any further injury during the apnea test. The patient should have a core body temperature of more than 35°C as hypothermia is a known cause of apnea.[4] Second, the patient should have a normal blood pressure for age. This can be achieved by assuring that the patient has an adequate circulating blood volume and that vasoactive agents have been adjusted to sufficiently support the patient's hemodynamics.[15] Contraindications to apnea testing include injuries that may result in apnea in the absence of brain death, such as a high cervical spine injury. Conditions that may make the apnea test unsafe to perform on a specific patient, such as severe hypoxemia due to acute lung injury, would be a contraindication to proceeding with apnea testing. If the patient's clinical status precludes the apnea test, an ancillary test may be used to assist in the determination of brain death.[4]

The technique for apnea testing can be variable from center to center. However, consensus guidelines recommend that the patient begin with a $PaCO_2$ and a pH in the normal range on an arterial blood gas sample.[4] This establishes a starting point for CO_2 measurement intervals; furthermore, if in a hypocarbic state, the patient is at increased risk for cardiovascular instability waiting for the $PaCO_2$ to increase.[17] Some children with chronic respiratory insufficiency may be hypercarbic at baseline and only respond to supranormal $PaCO_2$ levels. In this case, the $PaCO_2$ level should increase to $\geq$ 20 mm Hg above the baseline $PaCO_2$.[4] Then, patient should be preoxygenated with 100% oxygen for a period of time prior to the apnea test. The rationale for preoxygenation is to facilitate oxygenation, eliminate nitrogen stores, avoid desaturation, and prevent possible secondary cardiovascular effects.[16,17]

Once the patient has a normal $PaCO_2$ and is hyperoxygenated, the apnea test may commence. The patient is disconnected from the ventilator, or place in a mode that stops intermittent mandatory mechanical ventilation. Apneic oxygenation can be maintained by an insufflating cannula in the ETT, attaching a T piece to the ETT tube, or by attaching a self-inflating bag valve system, such as a Mapleson circuit connected to the ETT.[3,4] Continuous positive airway pressure (CPAP) mode on a ventilator has been used during the apnea test; however, many current model ventilators automatically change from CPAP to mandatory ventilation and deliver a breath when apnea is detected. Although some of these ventilators have adjustable allowed apnea times and trigger sensitivities that may be turned down, there have been false reports of spontaneous ventilation.[19] During the exam, the patient's chest and abdomen should be exposed to detect any chest wall movement or respiratory effort as the ventilator triggering and cardiorespiratory monitor tracing can detect air leak around the ETT or cardiac pulsations.[3] Examiners should continuously monitor the patient's heart rate, blood pressure, and oxygenation throughout the test. The patient should be observed for at least

8 to 10 minutes, if no movement is seen, a second blood gas is obtained. If the $PaCO_2$ rises 20 mm Hg above baseline and is $\geq$ 60 mm Hg without respiratory effort during the testing period, the apnea test is consistent with brain death.[3,4,15–17] If the $PaCO_2$ has not risen 20 mm Hg above baseline or is $\geq$ 60 mm Hg, a third blood gas may need to be obtained.

If, during the test, the patient's oxygen saturations fall below 85%, becomes hemodynamically unstable, or a $PaCO_2$ $>$ 60 mm Hg cannot be achieved, then the apnea test must be aborted and the patient should be stabilized through mechanical ventilation. The apnea test may be attempted again at a later time once normal oxygen saturations, normocarbia and hemodynamics stabilize, and normal parameters are obtained. Alternatively, ancillary studies may be obtained to aid in brain death determination. If any evidence of respiratory effort is observed, this is inconsistent with brain death and the apnea test should be immediately aborted.[4]

Brain death may be suspected in patients supported by extracorporeal membrane oxygenation (ECMO). However, there has been concern that CO_2 removal is done mainly by the ECMO membrane and that these patients are often more hemodynamically unstable.[20] Multiple recent small studies in adults and one in children have found a safe and valid means of performing the clinical exam and apnea test. The prerequisites of core body temperature and hemodynamics are easily controlled by the ECMO circuit, with addition of vasoactive medications if needed, to ensure a reliable exam. While traditional apnea test in these patients may not result in a sufficient rise in $PaCO_2$ given the efficient CO_2 removal by the membrane, the FiO_2 can be raised to 1.0 to preoxygenated the patient, and then, the ECMO sweep gas flow can be decreased to as low as possible to allow CO_2 rise without causing hypoxemia.[20–26] A novel pediatric case series found that a flow of 0.1 L/min for "smaller" children and 1 L/min for adult-sized children was well tolerated, and apnea test could successfully be completed.[22]

Ancillary Testing

Under current consensus guidelines, ancillary testing is not required to make a diagnosis of brain death, unless the neurological exam and apnea test cannot be completed. Examples of ancillary studies include electroencephalogram (EEG), four-vessel cerebral angiography determining cerebral blood flow (CBF), and radionucleotide CBF. These are not a substitute for the neurological exam.[4] Ancillary studies may be used to assist the examiner in diagnosing brain death to reduce the observation period when items of the neurological exam or apnea test cannot be completed safely due to the underlying medical condition of the patient, when there is uncertainty of the validity of the neurological exam, and when conditions, such as medication effects, may confound the examination and/or apnea test.[4] If an ancillary test is used because of the previously mentioned conditions, then all components of the exam performed initially should be complete and well documented. If an ancillary study is equivocal or there is concern about the validity of the study, the patient cannot be pronounced dead. The patient should continue to be observed until death can be declared by repeat physical exam and apnea test or a follow-up ancillary test can be performed. It is recommended to wait at least 24 hours for repeat examination or before repeat ancillary studies are performed.[4]

Declaration of Death

Death is declared upon confirmation and completion of two clinical exams and apnea tests. If ancillary tests are used, all components of the neurological examinations performed should be consistent with brain death.[4]

Special Considerations

Preterm and term neonates $<$ 7 days old were excluded from the 1987 guidelines due to the lack of data, concern for differences in physiology and reliability of ancillary testing. Concern has also been raised that the neurological examination may be difficult as some of the brain stem reflexes may not be completely developed.[4] Infants with anencephaly frequently have physical abnormalities, including ocular and otic congenital defects that prevent a complete neurological clinical exam from being performed. Since these patients lack a normally formed cerebrum, ancillary tests, such as EEG or CBF, are unable to be obtained. As such these infants cannot be declared brain dead.

Conflict of Interest
None.

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